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Beyond Anaemia: Diagnostic Challenges and Early Detection of Vitamin B12 Deficiency in Older Adults Living in Residential Aged-Care Facilities

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Abstract

Vitamin B12 (cobalamin) deficiency is an easily manageable and common deficiency in older people, often not suspected until anaemia is found; however, in residential aged care facilities (RACFs), it is often diagnosed only when anaemia is identified. This narrative review examines why anaemia is an unreliable gateway to diagnosis and how earlier detection might be achieved in residents. In this context, risk is focused by age-related and autoimmune gastric atrophy, long-term acid suppression, use of metformin, malnutrition and frailty. Clinical features are often neurological, cognitive or functional, and these features are often interpreted as dementia, ageing or polypharmacy. However, variable serum B12 levels and different assays, as well as the low sensitivity of intrinsic factor antibody and renal confounding of MMA, make diagnosis more difficult. The evidence suggests that a step-wise approach where the total or active B12 is interpreted against the assay-specific thresholds and metabolic markers in the grey zone are interpreted along with kidney function may be appropriate. We suggest admission screening, trigger-based testing, medication review and pragmatic treatment with outcome-based monitoring. There is a biochemically similar effect on high-dose oral therapy versus intramuscular therapy but limited clinical outcome data for older adults. Research priorities are facility-level prevalence data, screening pathways and trials with functional endpoints.

Keywords: *vitamin B12; cobalamin deficiency; older people; residential aged care; holotranscobalamin; methylmalonic acid; early detection; proton pump inhibitors.*

1. Introduction

Vitamin B12 (cobalamin) is a cofactor for two enzymes, methionine synthase and methylmalonyl-coenzyme A mutase, which are important for DNA synthesis and neurological function respectively [1]. Thus, deficiency not only impairs haematopoiesis, but also has a negative effect on the nervous system and is particularly prevalent in the elderly [2,3]. Population studies have shown that hypovitaminosis B12 is independently linked to adverse outcomes: low levels, defined as < 140 pmol/L, in the U.S. population of 24,262 adults in the National Health and Nutrition Examination Survey (NHANES) were associated with a modest but significant elevation in all-cause and cardiovascular mortality [4].

Conditions that are likely to cause deficiency are concentrated in residential aged-care facilities (RACFs). The prevalence of malnutrition in Australian residents is very high [5], with a pooled prevalence of about 27% among people with dementia in long-term care [6]; in a large cohort of New South Wales residents, 54% received a proton pump inhibitor (PPI) [7]. Residents also tend to be frail, have multiple medications and often are unable to accurately report on symptoms. However, clinical focus on B12 is frequently based on anaemia or

macrocytosis, leaving many affected individuals undiagnosed: a recent clinical review summarised by Cesana et al. [8] shows that in the majority of individuals with low B12 levels, neurological, neuropsychiatric or cognitive symptoms are the predominant clinical features, and less than 1 in 5 individuals may have anaemia [8,9].

Early detection is further hampered by lack of a gold standard test, thresholds and assay dependent results [2,8]. Pharmacists and prescribers are at the heart of prevention and identification of several principal risk factors, which are medicines. This review explores the reasons why residents of RACFs are at high risk, the ways in which deficiency manifests other than anaemia, the diagnostic issues that impede early detection and treatment and the possibility of pragmatic strategies to facilitate early detection and treatment in this context.

2. Scope and Approach

This is a narrative review. It focuses on publications since 2020, especially systematic reviews, RCTs, large cohort studies, laboratory medicine studies that evaluate the performance of diagnostic tests, and studies of medicines associated with deficiency and studies of medicines in institutional care, but only those relevant to older people. Information from direct observations in RACFs is limited, especially for current prevalence and screening results. The results of community-dwelling older adults, therefore, should be interpreted with care, and the recommendations made are merely evidence-informed proposals and not validated protocols.

3. Why Aged-Care Residents Are Vulnerable

The dietary B12 absorption requires gastric acid, intrinsic factor (IF) and a functional terminal ileum; a defect in the IF-mediated pathway is one of the commonest ways to develop a B12 deficiency [3]. Autoimmune gastritis (AIG), a growing immune-mediated disorder, is characterised by destruction of gastric parietal cells, loss of IF, and decreased acid production; it is often pauci-symptomatic or asymptomatic, and there are no screening strategies for AIG in place [10]. So, residents with undiagnosed AIG could go through years of silent malabsorption without being diagnosed, and a resident may continue to be deficient or become deficient over and over again and should then be followed up to look for the cause of the deficiency rather than given empirical treatment indefinitely.

Medicines add a modifiable layer of risk (Table 1). A PPI was found for 54% of 6439 people in 34 NSW nursing homes, most of whom had a PPI for more than 12 weeks and 27.1% had criteria for inappropriate overuse [7]. PPIs were prescribed to 44% of patients in German nursing homes, and there was no sufficient indication for these prescriptions in approximately 25% of cases [11]. A 2025 systematic review in older adults on polypharmacy noted that PPI long-term use results in decreased B12 and calcium levels [12], while a 2025 meta-analysis of serum B12 and homocysteine suggests conflicting opinions exist regarding PPI chronic use and the development of a B12 deficiency [13]. High-dose, long-term metformin use also hurts B12 status, though there are no clear recommendations for screening metformin users [14]. These risks are exacerbated by nutritional and functional factors. There is a high prevalence of malnutrition in Australian RACFs [5] and in individuals with dementia [6] and narrative evidence that there is a bi-directional link between low B12 levels and frailty, with low B12 potentially affecting the process of frailty, and frailty also affecting the bioavailability of B12 [15]. Figure 1 summarises these converging mechanisms that compromise vitamin B12 absorption and status in residents of aged-care facilities. Table 1 shows the principal contributors to vitamin B12 deficiency risk in residents of aged-care facilities.

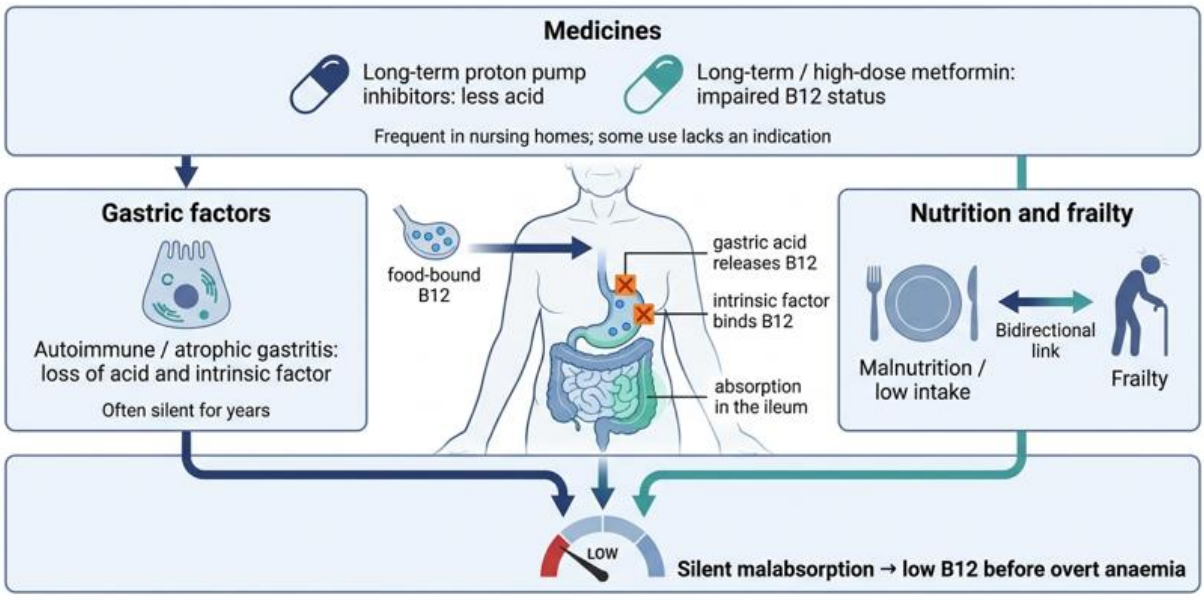

Figure 1. Converging mechanisms that compromise vitamin B12 absorption and status in residents of aged-care facilities: autoimmune and atrophic gastritis, acid-suppressing and glucose-lowering medicines, malnutrition and frailty.

Sources: Adapted from references [5,7,10,12,14,15].

Table 1. *Principal contributors to vitamin B12 deficiency risk in residents of aged-care facilities.*

Contributor	Mechanism	Key evidence relevant to older residents	Refs
Autoimmune/atrophic gastritis	Parietal cell destruction; loss of intrinsic factor and gastric acid	Increasingly prevalent; often asymptomatic or pauci-symptomatic; proactive screening lacking; intrinsic factor antibodies insensitive (32% sensitivity for corpus atrophic gastritis)	[10,16]
Long-term PPI use	Reduced gastric acid impairs release of food-bound B12	54% of 6,439 NSW nursing-home residents received a PPI, 27.1% inappropriate overuse; 44% prevalence in German nursing homes; systematic reviews report lower B12 but evidence conflicts	[7,11-13]
Metformin	Long-term or high-dose therapy impairs B12 status (multifactorial)	No definitive screening guidelines; deficiency frequently unrecognised	[14]
Malnutrition and low intake	Reduced intake of B12-containing foods	Malnutrition highly prevalent in Australian RACFs; pooled prevalence about 27% in people with dementia in long-term care	[5,6]
Frailty and multimorbidity	Bidirectional relationship; possible reduced bioavailability	Narrative evidence only; prospective data needed	[15]

4. Clinical Presentation Beyond Anaemia

The haematological signs are late and an unreliable marker. The classical presentation of macrocytic anaemia is not essential or sufficient for diagnosis: less than one in five people with low B12 had anaemia in the clinical review summarised above [8,9]. Neurological effects are sensory and motor dysfunction, ataxia, psychiatric disturbance and, in late stages, cognitive impairment evolving to dementia [3].

The cognitive signal is faint and easily confused. B12 and folate status were associated with memory and attention domains specific to cognitively healthy older adults [17]. For 4,464 NHANES participants aged 60 years and older, elevated circulating MMA was associated with worse cognition scores; however, this relationship was lost after adjusting for homocysteine and when individuals with hypertension and chronic kidney disease were excluded, indicating that this relationship was confounded by the presence of these comorbidities [18]. In RACFs with a high prevalence of dementia [6], or when the person is confused, lacks interest or is slow to react, misconceptions may be made about the person having a treatable deficiency, instead of a disorder that is a consequence of the dementia.

There is conflicting evidence regarding supplementation. A recent meta-analysis of 17 RCTs in 5275 older people showed no significant overall benefit from vitamin B6, B9 or B12 supplementation on the cognition score [19], while a smaller study in middle-aged and older adults with cognitive impairment showed vitamin B12 supplementation improved frontal function [20]. These findings suggest that the value lies in correcting true deficiency promptly rather than supplementing indiscriminately.

Functional outcomes may also be affected. Serum B12 has been shown to be positively correlated with total lean mass and appendicular lean mass in adults aged > 65 years [21] and B12 status has been associated with sarcopenia, cognitive disorders and frailty [15]. Low B12 levels have also been linked to increased all-cause mortality and previous NHANES analyses found that MMA was more strongly associated with impaired cognitive and physical function than serum B12 [4]. These are often blamed on ageing, leading to an overlooking of deficiency. Table 2 shows the Clinical presentation and why vitamin B12 deficiency is missed in older people. Figure 2 presents the anaemia “iceberg” in vitamin B12 deficiency.

Table 2. Clinical manifestations of vitamin B12 deficiency in older adults and reasons they are missed.

Domain	Presentation in older adults	Why deficiency is missed	Refs
Haematological	Macrocytic anaemia; late and inconsistent	Fewer than one in five people with low B12 present with anaemia, so a normal haemoglobin is falsely reassuring	[8,9]
Neurological and psychiatric	Sensory and motor dysfunction, ataxia, mood or psychiatric disturbance	Attributed to ageing, polypharmacy or neurodegeneration	[3]
Cognitive	Subtle memory and attention deficits; higher MMA linked to poorer cognitive scores	Overlaps with dementia, which is common in long-term care; MMA association confounded by homocysteine, hypertension and kidney disease	[6,17,18]
Functional and musculoskeletal	Lower lean mass and physical performance; links with sarcopenia and frailty	Seen as normal ageing; relationship with frailty is bidirectional	[15,21]
Prognostic	Serum B12 below 140 pmol/L associated with higher all-cause and cardiovascular mortality in NHANES	Risk is not visible at the bedside; requires biochemical testing	[4]

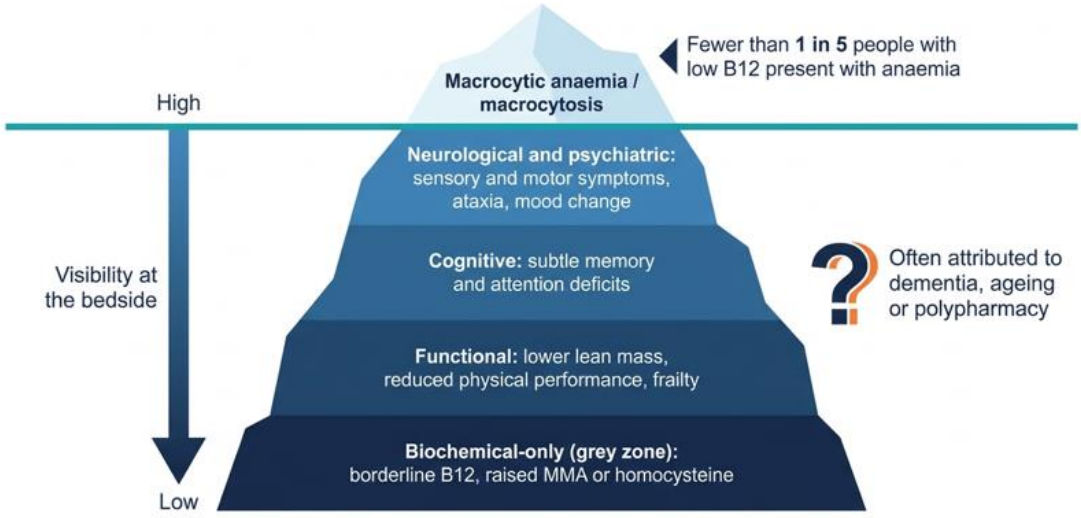

Figure 2. The anaemia "iceberg" in vitamin B12 deficiency: *macrocytic anaemia is the visible tip, whereas neuropsychiatric, cognitive, functional and biochemical-only presentations lie beneath the surface.*

Sources: Adapted concept from [2,8,9,17,18,21].

5. Diagnostic Challenges

No single laboratory marker is suitable for every patient [2]. The four tests used are: total serum B12, holotranscobalamin (holoTC, the "active" fraction), MMA and homocysteine. A composite indicator (4cB12) combining all four indicators and age has been suggested to enhance the recognition (Table 3) [1]. Using that framework, a score of −0.5 or worse is indicative of low B12 and/or possible subclinical symptoms, and a score of < −1.5 is suggestive or indicative of B12 deficiency [1].

The first obstacle is thresholds. The NICE guidance sets a total B12 deficiency at <180 ng/L and a B12 possible deficiency for further confirmation with MMA or homocysteine at 180-350 ng/L and considers total and active B12 as interchangeable first-line tests [8]. The 180 ng/L value, however, is based on expert consensus and older methods, and the reference populations were significantly younger (median about 45 years) than the reference populations typically tested (about 65 years), and the results from immunoassays were not interchangeable (Abbott over-estimated B12 and Beckman under-estimated B12 compared to Roche) [8]. The lower limits vary among

various analytical platforms [8,22] and the updated NICE guidelines have been described as a "challenging clinical and laboratory topic" [23]. Someone could thus get a “normal” result on one platform, but a different classification on another. One group tentatively suggested the NICE ranges converted to their respective platforms (e.g., ~204 ng/L for likely deficiency and ~379 ng/L as the upper limit of possible deficiency for a Roche platform) but noted the large confidence intervals and proposed that the upper limit of the interval be used to reduce the likelihood of false deficiency [8].

HoloTC is appealing due to its biologically active component. When applied to the older (age 50 years or older) women, holoTC performed best (0.93) compared to B12, MMA and homocysteine (0.88, 0.91 and 0.79, respectively); however, there was no clear superiority of one marker over total B12 in men or younger women [1]. Other assessments have also compared holoTC to other markers for deficiency [24].

In borderline cases of total B12, metabolic markers can be helpful; however, this population confounds these markers. MMA increases as the kidney function decreases and is associated with poor nutrition [25] while homocysteine is affected by folate, vitamin B6, thyroid function, and age, sex and glomerular filtration rate [1]. Interpretation, therefore, is dependent on renal function at the time of interpretation and a clear clinical question.

The cause is important since it will help determine the length of therapy. However, the antibodies are very specific but lack sensitivity: In 105 patients with corpus atrophic gastritis, a luciferase immunoprecipitation assay was 95% specific but only 32% sensitive and was independent of anaemia and B12 deficiency [16]. A negative antibody test does not rule out autoimmune gastritis, however. A proposed stepwise approach is summarised in figure 3. Table 3 shows the strengths and limitations of laboratory markers to assess vitamin B12 status in older residents.

Table 3. Laboratory markers used to assess vitamin B12 status: strengths and limitations in older residents.

Marker	Strengths	Limitations in older residents	Refs
Total serum B12	Widely available first-line test; NICE: below 180 ng/L deficiency, 180–350 ng/L possible deficiency	Thresholds derived in younger populations; assays not interchangeable; a normal value does not exclude deficiency	[2,8,22]
Holotranscobalamin (active B12)	Biologically active fraction; AUC 0.93 in women aged 50 years or older	No clear advantage over total B12 in men or younger women; availability varies	[1,24]
Methylmalonic acid (MMA)	Functional marker of tissue B12 status	Raised by reduced kidney function and poor nutritional status; association with cognition attenuated by confounders	[1,18,25]
Homocysteine	Functional marker; supports borderline results	Non-specific: affected by folate, vitamin B6, thyroid function, age, sex and kidney function; lowest AUC (0.79)	[1]
Intrinsic factor antibodies	Cause-finding in autoimmune gastritis; 95% specificity	Sensitivity only 32% for corpus atrophic gastritis; does not itself confirm deficiency	[10,16]
Combined indicator (4cB12)	Integrates holoTC, B12, MMA, homocysteine and age; values ≤ -0.5 suggest low B12 and < -1.5 possible or probable deficiency	Requires four assays; primarily a laboratory or research tool	[1]

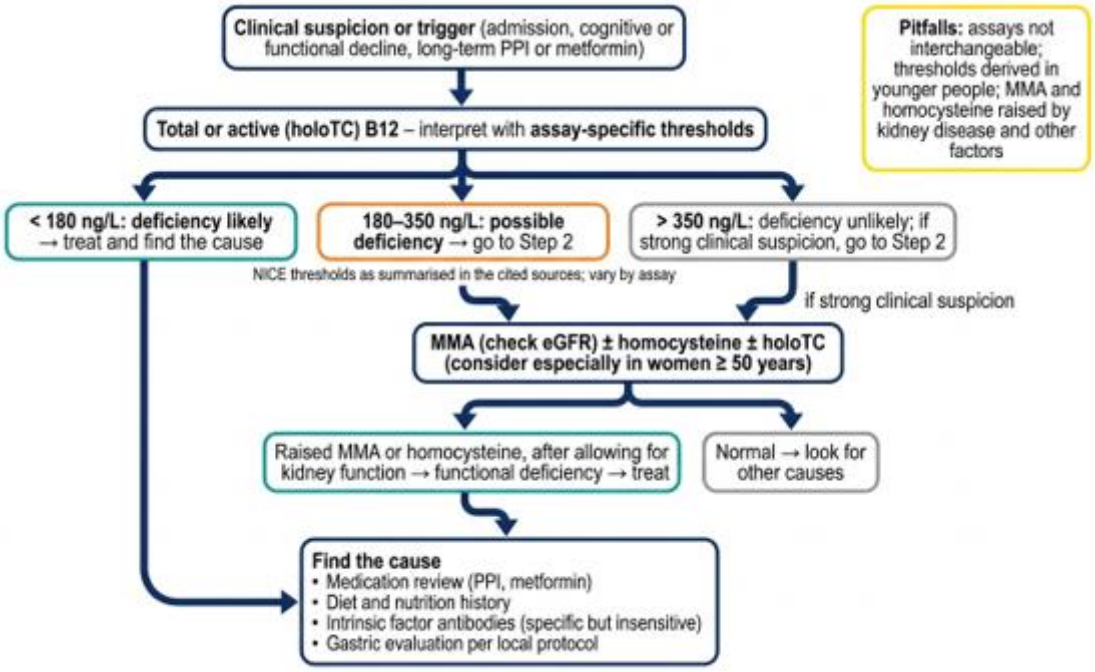

Figure 3. Proposed stepwise diagnostic approach to suspected vitamin B12 deficiency in aged-care residents, combining assay-specific total or active B12, metabolic markers interpreted with kidney function, and cause-finding

Sources: Adapted concept from references [1,2,8,16,25].

6. Early detection in Aged-Care Facilities

There is no validated screening pathway for RACFs and screening strategies trials were not found in RACF setting. Based on this evidence, a 3-layer model is suggested (Table 4, Figure 4). First, a baseline assessment on admission would include a medication history, dietary and GIT history, and a B12 level, evaluated using assay-specific thresholds [5,8]. The acid suppression, metformin use and malnutrition are clustered in this group and for this reason the admission is an efficient checkpoint.

Second, trigger-based testing should be integrated into routine care: new cognitive, neuropsychiatric, gait or functional decline, initiation or continuation of long-term PPI or metformin therapy and unexplained deficiency despite supplementation. Routine blood sampling to check B12 levels prior to diagnosing dementia or frailty is cheap and serves a potentially reversible contributing factor [17,20,21]. In the grey zone, adding MMA (with estimated GFR) or holoTC is warranted, especially in women > 50 years old [1,25]. An alternative is to repeat total B12 on the same platform, and to treat clinically in residents who are known to be at high risk, while seeking specialist advice when the picture is unclear, when there is limited access to MMA or holoTC.

Thirdly, medicines governance is a preventive instrument. Co-ordinated medication review and deprescribing of PPIs without a continuing indication could eliminate one modifiable risk factor, but there is ongoing debate regarding the causal link between PPI use and deficiency, with over a quarter of PPI use being classified as inappropriate in one large Australian cohort [7]. However, deprescribing should be considered in the context of actual indications: Of the same population, 38.5% of long-term users of bleeding-risk-increasing medicines were not prescribed a gastroprotective PPI [7] and the goal is not to decrease use, but the appropriate use. Metformin: There is no definitive guidance to monitor B12 routinely. In metformin, monitoring B12 periodically is recommended. All three layers can benefit from the support of pathology services with regard to reporting assay-specific thresholds [8].

Implementation will be dependent on facility workflow. The trigger is best identified by nurses, the medication review by pharmacists and the resulting treatment by general practitioners. Testing should be tied to a clear action, so that a borderline result is not disregarded or repeated for no good reason, and that the resident and/or their substitute decision-maker is involved in decisions regarding investigation and long-term therapy. The facilities should also ensure they are each using the same assay and thresholds with their pathology provider to ensure results are comparable if residents move between hospital and aged care. The following are elements of operation which are recommendations based on the diagnostic evidence above and have not yet been assessed in RACFs. Table 4 shows the proposed early detection of Vitamin B12 deficiency in aged care. Where Figure 4 presents the proposed early detection and monitoring pathway for RACFs.

Table 4. Proposed triggers, actions and supporting evidence for early detection of vitamin B12 deficiency in aged-care facilities.

Trigger or time point	Suggested action	Rationale	Refs
Admission	Baseline B12 (total or active) with medication, diet and gastrointestinal history; interpret using assay-specific thresholds	Risk factors concentrated in residents; thresholds vary by assay	[5,7,8]
Long-term PPI or metformin therapy	Periodic B12 re-check; structured medication review and deprescribing where no indication	Substantial inappropriate PPI use; no definitive metformin screening guidance	[7,13,14]
New or worsening cognitive, neuropsychiatric, gait or functional decline	Request B12 (with MMA or holoTC if borderline) before attributing decline to dementia or frailty	Subtle cognitive and functional associations; possibly reversible contributor	[17,18,20,21]
Borderline B12 result	Add MMA with kidney function, or holoTC; consider homocysteine	MMA and homocysteine are confounded by renal and other factors; holoTC may add value in women aged 50 years or older	[1,8,25]
Unexplained or recurrent deficiency	Intrinsic factor antibodies and gastric evaluation per local protocol	Autoimmune gastritis is often silent; antibodies are specific but insensitive	[10,16]
After treatment starts	Repeat biochemistry; reassess cognition, mobility and mood	Routes similar biochemically; clinical outcomes less certain	[3,26]

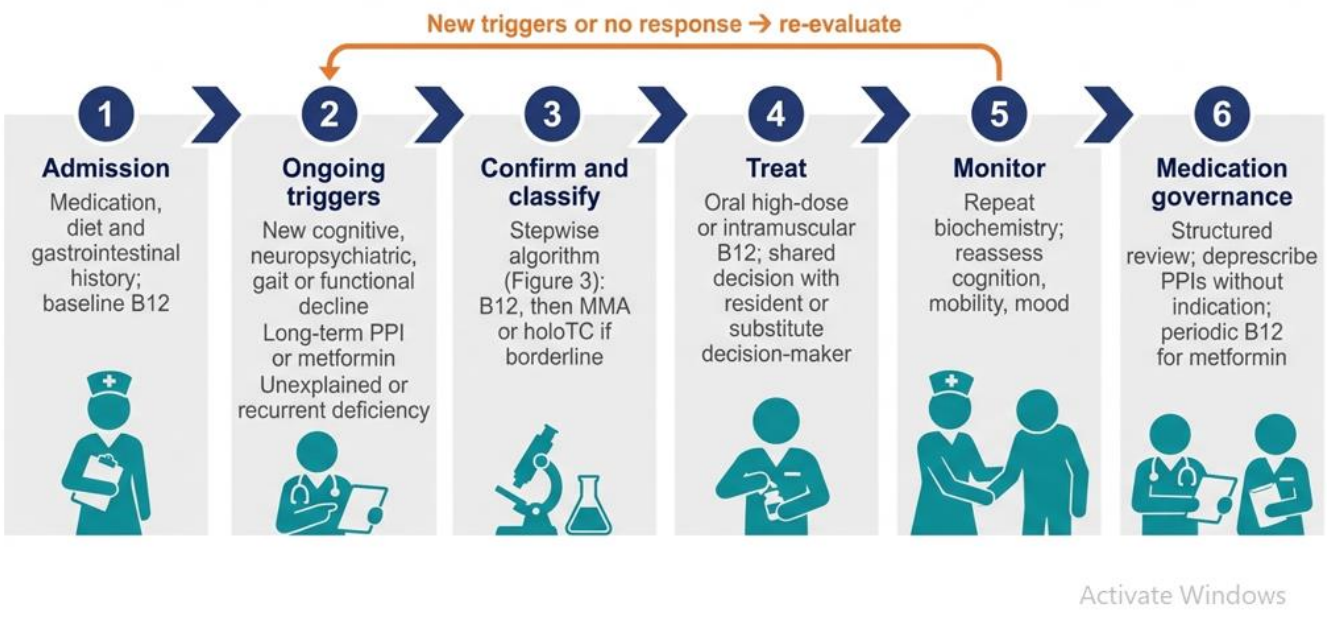

Figure 4. Proposed early detection and monitoring pathway for vitamin B12 deficiency in aged-care facilities, linking admission screening, trigger-based testing, diagnosis, treatment, monitoring and medication review

Sources: Adapted from references [3,7,8,14,26].

7. Treatment and Monitoring

There was no significant difference between the oral and the intramuscular treatment regimens in normalizing serum B12 levels at 8, 26, and 52 weeks in a pragmatic trial of 283 adults age 65 years or older with B12 deficiency [26]. A 2025 meta-analysis of 16 studies (6,098 people) also revealed no significant differences between the oral, sublingual and intramuscular forms of cobalamin or homocysteine, though there was a high degree of heterogeneity and publication bias [3]. Pharmacokinetic studies indicate that the fraction of vitamin absorbed decreases with increasing oral dose [27] and therefore, there should be a caution against assuming that larger oral doses will allow for a greater percentage of vitamin to be absorbed.

Less is known about clinical outcome data, like gait, cognition and function, which are biochemical. Specialist advice and tailored treatment is required for those who have severe neurological symptoms or those thought to have pernicious anaemia. Oral therapy may have practical benefits in RACFs because it avoids injections and clinic visits, while intramuscular therapy may be appropriate for residents with known malabsorption or for those who have a history of not taking their medication on time, and is most effectively decided upon between resident and the substitute decision-maker. Repeat biochemistry and re-assessment of cognition, mobility and mood should be monitored – not relying on haemoglobin. In NHANES, there was no association between higher intake from supplements and mortality, suggesting a good safety profile [4]. Residents and families need to be counselled that there is no guarantee of cognitive improvement; pooled trial evidence indicates that only a very modest cognitive benefit is achieved [19], and benefit is most likely to occur if a true deficiency is corrected early.

8. Knowledge Gaps and Future Directions

There are four gaps to be noted. First, there is limited characterisation of B12 deficiency and the grey zone in contemporary Australian RACFs. Second, age- and kidney-function-specific decision limits for both holoTC and MMA should be developed for the residents aged 80 years and older, who are underrepresented in the reference populations [8]. Third, prospective studies are needed to evaluate the effects of screening and trigger-based testing on cognitive, functional and quality-of-life outcomes, and effects of PPI deprescribing on B12 trajectory. Fourth, treatment trials should measure clinical endpoints not just serum B12 or homocysteine alone and should include dementia residents [3,19]. Feasibility, acceptability to residents and staff, and testing and follow-up costs should also be explored in implementation research. The review is limited in scope: the narrative design and the limited timeframe to 2020-2025, as well as the use of non-RACF populations for some conclusions.

9. Conclusion

Late and insensitive diagnosis of vitamin B12 deficiency in aged care through anaemia. Risk is concentrated in RACFs, including: gastric disease, acid suppressing drugs, metformin, malnutrition and frailty, presentations are neurological, cognitive and functional, so residents are likely to benefit from proactive, assay-aware testing at admission and clinical triggers; metabolic markers are used in borderline cases and interpreted in conjunction with kidney function. The treatment is relatively cheap and both oral and parenteral treatment seem to be biochemically similar. Pharmacists, nurses and general practitioners can have a combined focus on the modifiable factors, in this instance, medicine review, timely testing and follow-up for medicine therapy. The proposed care pathways must now be developed into evidence-based pathways based on facility-level data and outcomes.

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Conflict of Interest Statement

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All authors have read and approved the final manuscript and agreed to be accountable for all aspects of the work.

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